ABOUT THE AUTHOR

Aaron Wong, MD, FRCPC

Dr. Aaron Wong is the residency program director in the Department of Dermatology and Skin Science at UBC where he is also a clinical assistant professor. His clinic is based at St. Paul's Hospital and focuses on HIV Dermatology and he also has a community practice in New Westminster, B.C.

CASE FOR CONSIDERATION: A 30-YEAR-OLD HIV-POSITIVE MAN WITH PSORIASIS

You are seeing a 30-year-old man with a history of established psoriasis in your outpatient dermatology clinic. The patient has well-controlled human immunodeficiency virus (HIV) and he takes a new antiretroviral (ARV) medication, Biktarvy®. The patient's HIV in the blood is undetectable and his CD4 T-cell count is normal. His health is otherwise good. During the clinical workup, he mentions that his partner is HIV-negative and is on pre-exposure prophylaxis (PrEP) medication and has developed brown facial spots and is wondering if the PrEP medication may have caused this and also wants to see a dermatologist.

The patient starts on combination calcipotriene / betamethasone dipropionate foam and considers phototherapy. Upon reviewing the data on Biktarvy®, you become aware that it causes "rash" and wonder about interactions with acitretin, cyclosporine, or methotrexate. Biktarvy® contains bictegravir, emtricitabine and tenofovir alenamide. It does not contain ritonavir.

HIV and its treatment have changed significantly over the past 30 years. The virus can be fully suppressed with antiretroviral therapy (ARV), formerly known as highly active antiretroviral therapy (HAART). If ARVs are accessible and started early, collaborative cohort studies across Europe and North America demonstrate improved survival & life expectancy. There are now no threshold levels for initiation of ARVs based on CD4 T-cell count or viral load, if the ARVs are accessible to the patient. Treatment is generally recommended after diagnosis of HIV.[25]

Questions to Ponder:

- What are the relevant updates with regard to the newer anti-retroviral therapies and acronyms?
- Should we be concerned about intralesional or topical steroids and protease inhibitors such as ritonavir?
- What about using systemic medications such as acitretin, methotrexate, and cyclosporine together with ARVs?

Updates in HIV Acronyms

HIV-related cutaneous reactions can be due to initial infection with the virus itself, opportunistic infections (OI), or because of treatment of the virus or OIs themselves.

Immune reconstitution inflammatory syndrome (IRIS) is a phenomenon whereby the inflammatory response is exaggerated towards an infectious organism as host immunity recovers (i.e. T helper or CD4+ cells increase) following treatment with ARVs. Those diagnosed at a later stage of HIV are more susceptible and typically this can manifest in the form of extensive infections such as herpes simplex virus infections, herpes zoster, warts, molluscum, candida, and dermatophyte infections. Non-infectious sequalae can include lupus, extensive alopecia areata, or folliculitis.[1]

The use of PrEP in landmark, well-conducted randomized controlled trials have demonstrated efficacy of combination tenofovir disoproxil fumarate and emtricitabine (TDF-FTC or Truvada®) in preventing HIV transmission and has been approved by Health Canada for this indication.[2-4]

Post-exposure prophylaxis (PEP) can be non-occupational (nPEP) or occupational. Combination tenofovir disoproxil fumarate and emtricitabine (generic or branded Truvada®) is also used for this purpose. Lifestyle and behavioral interventions still remain key to HIV prevention even with the availability of PEP and PrEP.[5]

Antiretrovirals – New and Old

HIV antiretroviral therapy has consisted of combinations of the following[8]:

1) Nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTI)
2) Non-nucleoside reverse transcriptase inhibitors (NNRTI)
3) Protease inhibitor (PI)
4) Integrase inhibitors
5) CCR5 antagonists

Antiretroviral therapy has moved towards combining different types of ARVs into one convenient pill, taken once a day including branded medications such as:

- Genvoya® (elvitegravir + cobicistat + emtricitabine + tenofovir alafenamide)
- Odefsey® (emtricitabine + rilpivirine + tenofovir alafenamide)
- Biktarvy® (bictegravir + emtricitabine + tenofovir alafenamide)
- Stribild® (cobicistat + elvitegravir + emtricitabine + tenofovir disoproxil)
- Atripla® (efavirenz + emtricitabine + tenofovir disoproxil)
- Complera® (emtricitabine + rilpivirine + tenofovir disoproxil)

Many of the newest QD regimens contain the nucleotide reverse transcriptase inhibitor (NRTI), tenofovir alafenamide (TAF), instead of tenofovir disoproxil fumarate (TDF). TAF has some advantages over TDF, including selectively activating within the cell (whereas TDF activates in the bloodstream), less nephrotoxicity & less reduction in bone mineral density. TDF, however, may lead to less elevations of cholesterol and may be beneficial in those with dyslipidemia.[6,7]

Generally, most ARVs are well-tolerated by patients and mucocutaneous adverse events tend to be the exception, rather than the norm. Non-nucleoside reverse transcriptase inhibitors (NNRTI) are the most common class of ARVs to cause cutaneous toxicity, particularly morbilliform eruption. The morbilliform eruption tends to resolve even when the medication is continued; thus, physicians can treat through the rash with agreeable patients. Nevirapine, in particular, has been associated with morbilliform eruption, drug hypersensitivity and Stevens–Johnson syndrome/ toxic epidermal necrolysis (SJS/ TEN).[9] In the developing world, nevirapine is a common cause of SJS / TEN in HIV / AIDS patients. The observed cluster of adverse

events recorded as "rash" were used non-specifically in clinical trials that formed the basis for bringing these drugs to market, so characterization of cutaneous adverse events remains imprecise for many of these medications.

HIV & Lipodystrophy

Antiretroviral lipodystrophy manifests through a variety of changes in body and facial fat composition. Metabolic abnormalities often accompany the lipodystrophy including dyslipidemia and impaired glucose tolerance. Lipoatrophy occurs in the facial temporal and buccal fat pads, limbs and buttocks while lipohypertrophy occurs in the abdomen, dorsocervical region ("buffalo hump"), and breast tissue (gynecomastia). These findings were initially attributed to protease inhibitors (PI) but now are strongly related to NRTIs, particularly stavudine and didanosine as well as NNRTIs such as efavirenz.[10,11,13]

Protease Inhibitor Drug Interactions

Ritonavir is protease inhibitor that boosts the function of other PIs by inhibition of the cytochrome P450 3A4 pathway. This inhibition reduces breakdown of other PIs, thus providing the aforementioned "boosting" effect. Other drugs metabolized by this pathway, such as corticosteroids and cyclosporine, both of which are used with relative frequency in dermatology, should be approached with caution. Iatrogenic Cushing's syndrome (ICS) has been reported with single epidural, intra-articular or intramuscular injections of 40 mg or more of triamcinolone acetonide (TAC). There are no published reports of this occurring with intralesional or topical corticosteroids. However, iatrogenic Cushing's syndrome can occur with topical steroids in patients without HIV so the effects of ritonavir should not be disregarded.[14-16]

There are currently no guidelines or data to suggest a safe dose. Consultation with the patient's HIV provider to determine if an alternate, non-boosted regimen is advisable if intralesional therapy is being considered, particularly if the anticipated dosage is large or injections are to be given on a regular basis. If intralesional therapy is initiated, the author suggests dilution of the TAC to 2.5 mg / ml or lower, keeping the total administered dose below 15 mg and spacing out injections by 8-12 weeks. If there is a clinical suspicion of adrenal suppression or iatrogenic Cushing's syndrome, these patients should be further investigated.

Cyclosporine is similarly affected by ritonavir-induced cytochrome P450 3A4 inhibition. Lower doses and monitoring of cyclosporine levels may be necessary to prevent toxicity if it must be used. Based on pharmacokinetic data, daily doses of cyclosporine should be

Table 1.
Mucocutaneous adverse events of anti-retroviral therapy.[10,11,12]

DRUG CLASS	COMMON MUCOCUTANEOUS FINDINGS
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI)	
Zidovudine	Nail & mucous membrane hyperpigmentation
Abacavir*	Abacavir hypersensitivity syndrome: "maculo-papular rash", urticaria, diffuse erythema, erythema multiforme, targetoid eruption, morbilliform eruption, drug reaction with eosinophilia and systemic symptoms (DRESS), drug hypersensitivity syndrome, Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN) *Screening for HLA B5701 allele positivity significantly reduces development of the abacavir hypersensitivity syndrome
Stavudine	Lipodystrophy
Emtricitabine	Xerosis and eruptions of various morphology (macules-papules, vesicular, pustular)
NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS	
Tenofovir	Self-limited rash with morbilliform eruption, vesicular eruptions & urticaria; overall incidence is low
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI)	
Nevirapine	Morbilliform eruption (up to 28%) and DRESS, SJS, TEN; oral ulcers & acute generalized exanthematous pustulosis
Efavirenz	Morbilliform eruption
Etravirine	Morbilliform eruption
PROTEASE INHIBITORS (PI)	
Ritonavir	Circumoral paresthesia
Fosempranavir	Morbilliform eruption; drug contains a sulfa moiety
Atazanavir	Jaundice & scleral icterus (due to increased unconjugated bilirubin)
Darunavir	Self-limited morbilliform eruption
Indinavir	Morbilliform eruptions, retinoid like effects (hairloss, cheilitis, xerosis & paronychia) and lipohypertrophy; not commonly used
INTEGRASE INHIBITORS	
Elvitegravir	Not commonly reported with this group
Bictegravir	
Raltegravir	
ENTRY & CCR5 FUSION INHIBITORS	
Enfuvirtide	Injection site reactions
Maraviroc	Undefined "rash" in up to 16.5% in preclinical trial

reduced by 5-20%. This poses a challenge for weight-based dosing of cyclosporine which may range from 2-5 mg / kg, depending on the indication. The old adage of "start low, go slow" should be adopted, along with the monitoring of levels when ritonavir and cyclosporine are being used concomitantly.[17]
Stribild® contains cobicistat, elvitegravir, emtricitabine and tenofovir. Cobicistat is also a cytochrome P450 3A4 (CYP3A4) inhibitor and there have been reports of adrenal suppression with concurrent inhaled, intranasal or intra-articular corticosteroids.[18,19]

Other Systemic Medications and HIV

Acitretin is an established immune-modulating retinoid for treatment of psoriasis in HIV. It is not metabolized through the cytochrome P450 pathway.[20] Methotrexate (MTX) use in HIV showed poor safety outcomes or opportunistic infections in the published literature from 1987-1995.[21-24] This was before advent of regular ARV therapy and thus, patients may have had poorly controlled HIV. In some cases, methotrexate doses were higher than what is normally used in dermatology. If the patient has well controlled HIV, MTX can be used provided that regular clinical and laboratory monitoring are followed. Online drug interaction checkers are helpful as well.

Summary

HIV treatments have come a long way and there continue to be medical advances which generally herald improved outcomes for patients, but adverse cutaneous events from existing and new medications should not be overlooked.

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